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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,863	11/03/2003	Balaram Ghosh	C261 1030.1	9355

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EXAMINER	
FLOOD, MICHELE C	

ART UNIT	PAPER NUMBER
1655	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,863	GHOSH ET AL.	
	Examiner	Art Unit	
	Michele Flood	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on July 26, 2005.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The objection to the specification made in the previous Office action has been overcome by Applicant's amendment.

The rejection made under 35 U.S.C. 112, second paragraph, has been overcome by Applicant's amendment.

Claims 1-13 are under examination.

Response to Arguments

Claim Rejections - 35 USC § 102

Claims 1-10 and 12-13 is/are/remain rejected under 35 U.S.C. 102(b) as being anticipated by Aoyama et al. (N). Applicant's arguments have been fully considered. However, the rejection stands for the reasons set forth in the previous Office action and for the reasons set forth below.

Applicant claims a method of preventing and/or treating asthma in animals including humans using natural compound luteolin, said method comprising administering a composition consisting essentially of a therapeutically effective dose of the luteolin to the animal.

Applicant's main argument is directed to the idea that the amendment to Claim 1 overcomes the teachings of Aoyama because "Aoyama does not disclose what a therapeutic amount of any single compound in the disclosed extract may be, let alone what an effective amount of luteolin might be." Applicant also argues that the cited reference fails to anticipate the claimed subject matter because the *Perilla* seed extract taught by Aoyama contains luteolin and additional compounds; and, thus Applicant mistakenly submits that Aoyama neither teaches nor suggests compositions consisting essentially of luteolin. However, Applicant's arguments are not persuasive because Aoyama teaches a method of preventing and/or treating asthma in animals comprising orally administering an effective amount of an alcoholic extract obtained from the *Perilla* seed, which comprises luteolin. Aoyama teaches the reference extract as a histamine release inhibitor, which is extremely good in action of inhibiting the release of histamine or the development of asthmatic features comprising Early Airway Response (EAR). In [0027], Aoyama teaches administering 0.5-3000 mg/day of the reference extract or 0.3 to 15% weight percent or 0.01-10 weight percent to a patient in need thereof of treatment. Furthermore, Aoyama expressly teaches each of apigenin, chrysoeriol, luteolin and rosmarinic acid as histamine release inhibitors, as well as *Perilla* seed alcohol extracts containing the aforementioned compounds and an EtOAc fraction of *Perilla* seed extract as inhibitors of histamine release, which are useful in the prevention and/or treatment of allergic disease conditions, such as asthma.

Contrary to Applicant's argument that Aoyama does not teach treatment of asthma comprising the administration of a composition consisting essentially of luteolin,

Aoyama expressly teaches that the bioactive compounds contained in the disclosed *Perilla* seed extract can be concentrated, condensed or isolated from the plant seed extract, in [0020] through [0023]. Aoyama also teaches that while the referenced extracts are considered as histamine release inhibitors, refining of the active principle compounds contained therein the extracts can be isolated and that fractions with the highest activity can be collected and used as histamine release inhibitors for treatments or prophylaxis of allergic diseases, such as asthma. In [0031], Aoyama teaches a method of isolating luteolin from *Perilla* seed extract. Hence, the method of treatment taught by Aoyama is not only directed to the administration of effective amounts of *Perilla* seed extract or fractions thereof comprising luteolin but also the administration of effective amounts of each of the individual compounds contained therein (including luteolin) to provide the claimed beneficial functional effect for the claim-designated disease condition. *See* [0010], wherein Aoyama expressly teaches that each of apigenin, chrysoeriol, luteolin and rosmarinic acid may be efficiently extracted from the seed extract and used in the making of therapeutic preparations for oral administration. Applicant is also directed to [0006] wherein Aoyama clearly teaches that that the disclosed compositions useful for treating and/or preventing asthma may consist essentially of one or more of the disclosed histamine release inhibitors, such as luteolin. Again, the Office points to [0027] wherein Aoyama clearly teaches the effective dose range amounts of the histamine release inhibitors for the making of oral pharmaceuticals to be administered to patients in the treatment or allergic diseases, such as asthma: "0.5-3000 mg is usually suitable for in an adult, although a dose may

change with the age or a medication method, condition of disease, and a patient etc. at 0.5-500 mg and a child as an active principle per day ...". Furthermore, in [0029], Aoyama expressly teaches that the referenced histamine isolation inhibitors can substantially reduce an allergic response, such as cellular degranulation (an asthmatic feature of Late Airway Response). For instance, Aoyama teaches, "Therefore, the histamine isolation inhibitor of this invention can treat or prevent effectively the pollinosis which is many symptoms of I-beam allergy, asthma, dry grass heat, rhinitis, urticaria, a drug allergy, etc. Moreover, it becomes possible to prevent allergy in an every day life and to improve a body easily with the allergy prevention external preparations and allergy prevention food containing the histamine isolation inhibitor of this invention." Moreover, Aoyama clearly teaches that the administration of the referenced compounds, including luteolin, and extracts or fractions thereof comprising luteolin inhibit the release of histamine, which is a symptomatic developmental feature of EAR; and, as set forth immediately above, Aoyama clearly teaches that the referenced histamine isolation inhibitors substantially reduce cellular degranulation, which is a symptomatic developmental feature of LAR. In [0002] - [0003], Aoyama also clearly describes the progressive biomechanisms that lead to the development of allergic responses in allergic disease, such as asthma, and expressly teaches that by controlling or suppressing the release of histamine, one may also prevent symptoms of LAR, *e.g.,* the production of mast cells and IgE. Since, the administration of effective amounts of the compositions taught by Aoyama inhibits the release of histamine, the

method of treatment taught by Aoyama would indeed prevent the development of asthmatic features comprising both EAR and LAR.

Finally, while Applicant may continue to argue that Aoyama does not expressly teach that the referenced method of treatment prevents development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, or any of the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level, or wherein luteolin inhibits airway constriction or airway hyperactivity, *per se*. However, the method of treatment taught by Aoyama comprises the oral administration of the same ingredient in the same amounts to provide the same beneficial functional effect for the prevention of asthma in patients in need thereof of such treatment. Therefore, the claimed functional effects for the prevention of the development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, and the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level and the inhibition of airway constriction and airway hyperactivity are inherent to the method of treatment taught by Aoyama.

The reference anticipates the claimed subject matter.

Claims 1-13, as amended, is/are/remain rejected under 35 U.S.C. 102(b) as being anticipated by Wang (U), as evidenced by the teachings of Peng (V and/or W, translation of foreign language non-patent literature provided herein.) Applicant's

arguments have been fully considered. However, the rejection stands for the reasons set forth in the previous Office action and for the reasons set forth below.

Applicant states, "Wang discloses that luteolin is effective at treating bronchitis, and the various symptoms associated with bronchitis. While asthma is a symptom of bronchitis, bronchitis is not a symptom of asthma." Thus, Applicant reasonably argues that Wang's method of treating patients with asthma associated with bronchitis comprising the administration of effective dose amounts of a composition consisting essentially of luteolin "does not necessarily lead one to the conclusion that all asthma patients, including those not suffering from bronchitis, would be effectively treated by luteolin." However, Applicant's argument is not found fully persuasive because Wang expressly teaches a method of orally administering an effective amount of luteolin obtained from plant sources (120 mg/day p.o.) for 10 days to patients with bronchitis. On page 148, Column 2, under "*Clinical Studies*", Wang teaches, "The major symptoms of chronic bronchitis, including cough, asthma, sputum and wheezing, were effectively alleviated with luteolin treatment (Table VI). No liver, cardiac or renal toxicity was reported." Table VI further indicates a rate of 93.3% complete remission of asthma symptoms in bronchitis patients treated with luteolin. Thus, while Applicant argues, "It is not clear that bronchitis treatments are effective at treating asthma patients, except perhaps those suffering from asthma associated with bronchitis", the Office notes that dependent Claim 1 is directed to a method of treating asthma in animals comprising the administration of an effective amount of luteolin; and, thereby does not preclude the treatment of asthma in patients suffering other disease conditions such as those

patients with asthma associated with bronchitis as treated by the method taught by Wang. Therefore, absent evidence to the contrary, Wang clearly teaches the claimed method of treatment since the data presented in Table VI demonstrates that asthma in bronchitis patients was alleviated by luteolin treatment.

Thus, while Wang does not expressly teach that the referenced method of treatment prevents development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, or any of the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level, or wherein luteolin inhibits airway constriction or airway hyperactivity, *per se*, the method of treatment taught by Wang comprises the oral administration of the same ingredient in the same amounts to provide the same beneficial functional effect for at least the treatment of asthma in patients suffering bronchitis and in need thereof of such treatment. Therefore, the claimed functional effects for the prevention of the development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, and the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level and the inhibition of airway constriction and airway hyperactivity are inherent to the method of treatment taught by Wang, especially in view of Wang teaching that luteolin treatment provided a rate of 93.3% complete remission of asthma symptoms in bronchitis patients treated with luteolin.

Applicant may continue to assert that the rejection made herein is improper because the Office has not provided a reference teaching that bronchitis treatments are

effective at treating asthma patients; however, the Office directs Applicant to the teachings of Peng et al., set forth immediately below, wherein Peng proves that the administration of effective dose amounts of a composition consisting essentially of luteolin is effective for treating animals with either bronchitis or asthma. Thus, while it may be true that not all drugs used for the treatment of bronchitis are effective at treating asthma patients and/or asthma patients with bronchitis, Peng clearly discloses that luteolin is effective in treating patients with either asthma or bronchitis.

The reference anticipates the claimed subject matter.

Claims 1-3 and 12-13, as amended, is/are/remain rejected under 35 U.S.C. 102(b) as being anticipated by Peng et al. (V and/or W). Newly applied as necessitated by amendment.

Peng teaches a method of treating asthma comprising orally administering a composition consisting essentially of luteolin to animals. On page 3 of the translated document, first paragraph, Peng teaches that an herbal extract of *Ajuga decumbens* Thumb., wherein the active principle is luteolin, has been used for the treatment of both bronchitis and asthma. On pages 11 and 12 of the translated document, under "*Effect of Luteolin on Isolated Guinea Pig Trachea*" and "*Effect of Luteolin on Muscle Tonicity of Guinea Pig Bronchus*", Peng teaches that effective amounts of luteolin can antagonize the effect of histamine and can relax the animal bronchus and microbronchus smooth muscles.

The reference anticipates the claimed subject matter.

Claims 1-13, as amended, is/are/remain rejected under 35 U.S.C. 102(b) as being anticipated by Nagai et al. (X and/or U1, translation of foreign language non-patent literature provided herein.). Newly applied as necessitated by amendment.

Applicant argues that Nagai teaches that luteolin inhibits histamine but does not teach or suggest that it can be used to treat asthma. However, this is not persuasive because Nagai investigated the effects of an oriental-medical preparation comprising luteolin, *i.e.,* Sho-seiryu-to, and luteolin on bi-phase allergic reactions mediated by IgE. Nagai teaches administering Sho-seiryu-to once only or daily for a week significantly inhibited both immediate (Early Airway Response, EAR) and late phase reactions (Late Airway Response, LAR) in mice sensitized with anti-DNP monoclonal IgE antibodies and DNP antigen. For example, Nagai teaches, "In immediate-phase instances, Sho-seiryu-to is thought to have effected inhibition by antagonistic operations against mediators, such as histamines released from mast cells. In late-phase cases, it is thought to have inhibited by suppressing the production and operation of cytokines [such] as TNF-alpha." *See* Figure 19, wherein Nagai shows that the administration of effective amounts of Sho-seiryu-to to an experimental system of guinea pig bronchial asthma-like model inhibited both instant and delayed phases. Similarly, Nagai teaches that administration of small quantities of luteolin demonstrated significant inhibitory effects on both immediate- and late-phase reaction, as well as, the release of histamine. *See* page 2 of translation, last paragraph, bridging page 3. On page 9 of the translated document, second and third paragraphs, Nagai further teaches that allergic reactions and clinical symptoms of bronchial asthma are divided into immediate-phase reactions

and late-phase reactions wherein bronchial asthma has immediate-phase attack and late-phase asthma attack. Also *see* Figure 2. With particular regard to the administration of luteolin, Nagai demonstrates that administration of plant luteolin derived from plants to animals showed significant inhibiting effects on the immediate phase and the late phase from low dosages of 0.1mg/kg, and showed strong inhibition of the late phase in particular (see Figure 29); luteolin showed extremely strong histamine release-inhibiting effect (see Figure 30); luteolin showed very strong inhibiting effect on TNF-∝ and IL-6 (see Figure 31); and luteolin showed inhibiting effect of release of arachidonic acid metabolites from mast cells (see Figure 32). Finally, on page 50 of the translation, second paragraph, Nagai teaches, "From the fact that luteolin shows a strong inhibiting effect on histamine release from mast cells and cytokine production, the inhibition of immediate phase and late phase in allergic reactions with IgE-dependent mast cells as the crux was conjectured."

The reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

Claims 1-13, as amended, is/are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Nagai et al. (X and/or U1) in view of Aoyama et al. (N). Newly applied as necessitated by amendment.

The teachings of Nagai are set forth above. While Nagai expressly teaches a method of treating asthma in animals comprising administering a composition consisting essentially of luteolin, Nagai does not teach a method of treating asthma in humans comprising the administration of a therapeutically effective dose of luteolin to humans *per se*. However, it would have been obvious to one of ordinary skill in the art to apply the method of treating asthma in animals comprising administering a therapeutically effective dose of luteolin taught by Nagai to humans to provide the instantly claimed invention because at the time the invention was made Nagai taught that while the administration of compositions consisting essentially of luteolin to an experimental system of guinea pig bronchial asthma-like model inhibited both instant and delayed phases and although luteolin strongly inhibited mouse IgE-dependent dual-phase allergic reactions due to inhibition of mast cell activation, Nagai noted that the mast cell systems of mice and rats while sharing similarities to human mast cells differ in various details; and, therefore, Nagai investigated the effects of luteolin on dual-phase allergic reaction using human mast cells for clinical application. Based on the data for the administration of luteolin to human mast cells, Nagai concluded, on page 50 of the translation, second paragraph, Nagai teaches, "From the fact that luteolin shows a strong inhibiting effect on histamine release from mast cells and cytokine production,

the inhibition of immediate phase and late phase in allergic reactions with IgE-dependent mast cells as the crux was conjectured." Hence, at the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to apply the method of treating asthma in animals comprising administering a therapeutically effective dose of luteolin taught by Nagai to provide the instantly claimed method of treating and/or preventing asthma in a human because Nagai clearly teaches the beneficial effects of luteolin treatment on human IgE-dependent mast cells in late phase of allergic reactions and Nagai teaches that crude drugs comprising luteolin as a bioactive component are known in the art of Chinese Traditional Medicine as being useful in the treatment of bronchial asthma and that the individual herbs comprising the crude drugs, such as *Perilla* and *Scutelleria*, were found to show strong inhibitory effects on the double-phase allergic reactions of the instant and delayed phases, wherein luteolin was found to be the bioactive compound providing such inhibitory activities. Thus, it would have been well in the purview of one of ordinary skill in the art at the time the invention was made to adjust the therapeutic dose amounts of luteolin used in the method of treating asthma in animals taught by Nagai to provide a method of treating and/or preventing asthma in humans because Nagai teaches the inhibitory effects of luteolin on the biomechanisms involved in human mast cell activation and suggests that drugs which inhibit inflammatory cytokines, such as IL-4, IL-5, can late-phase reactions and the progress of allergic inflammation disease conditions, such as asthma in humans. *See* Figure 1.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 1-13, as amended, remain rejected under 35 U.S.C. 102(b) as anticipated by Aoyama et al. (N) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Aoyama et al. (N) in view of Nagai (X and/or U1), Kimata et al. (V1). Newly applied as necessitated by amendment.

The teachings of Aoyama were set forth above. Applicant argues that Aoyama does not teach an effective dose of luteolin, or that the composition would be effective without the other components of the extract. Thus, Applicant concludes, "On this basis alone, the instant claims, directed to a composition consisting essentially of luteolin, are not obvious over Aoyama." However, Applicant's arguments are not persuasive because, as set forth above, Aoyama clearly teaches a method of preventing and/or treating asthma in animals including humans comprising the administration of a composition consisting essentially of a therapeutically effective of luteolin.

The claims are drawn to a method of preventing and/or treating asthma in animals including humans comprising administering composition consisting essentially of a therapeutically effective dose of the luteolin to the animal; wherein the method shows no side effects; wherein the luteolin is administered orally; wherein the development of Early Airway Response and Late Airway Response are prevented; wherein levels of IFN-gamma, IL-5, IL-4 and IgE are modified to a normal level; wherein

the duration of administering luteolin ranges between 5 to 10 days; and, wherein luteolin inhibits airway constriction and airway hyperactivity.

Aoyama teaches a method of preventing and/or treating asthma in animals comprising orally administering an effective amount of an alcoholic extract obtained from the *Perilla* seed, which comprises luteolin or a composition consisting essentially of luteolin. Aoyama teaches the reference extract as a histamine release inhibitor, which is extremely good in action of inhibiting the release of histamine or the development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response (LAR). Furthermore, Aoyama expressly teaches each of apigenin, chrysoeriol, luteolin and rosmarinic acid as histamine release inhibitors, as well as *Perilla* seed alcohol extracts containing the aforementioned compounds and an EtOAc fraction of *Perilla* seed extract as inhibitors of histamine release, which are useful in the prevention and/or treatment of allergic disease conditions, such as asthma. In [0027], Aoyama teaches administering 0.5-3000 mg/day of the reference extract or 0.3 to 15% weight percent or 0.01-10 weight percent to a patient in need thereof of treatment. Although Aoyama does not expressly teach that the reference method for prophylaxis and/or treatment of asthma in animals comprising administering a composition consisting essentially of luteolin encompasses modifying levels of IFN-gamma, IL-5, IL-4 and IgE to a normal level and inhibiting airway constriction and airway hyperactivity, the claimed functional effects are inherent to the method taught by Aoyama since the instantly claimed method is a one-step process of administering a therapeutic dose of a composition consisting essentially of luteolin to a patient in need of prevention and/or

treatment of asthma, and since the ingredient, the amount of the ingredient, and the route of administration for the delivery of the ingredient are the same as instantly claimed by Applicant. Thus, a method of preventing and/or treating asthma in animals including humans using a composition consisting essential of a therapeutically effective dose of natural compound luteolin wherein level of IFN-gamma increases to normal level, wherein level of IL-5 decreases to normal level, wherein level of IL-4 decreases to normal level, wherein level of IgE decreases to normal a level, and wherein luteolin inhibits airway constriction and inhibits airway hyperactivity is inherent to the method taught by Aoyama. The cited reference discloses a method of preventing and/or treating asthma in animals comprising administering an effective amount of a composition consisting essentially of a therapeutically dose of luteolin - - which appears to be identical to the presently claimed method, since the method taught by Aoyama prevents and/or treats asthma in animals in need thereof comprising the administration of therapeutic amounts of a composition consisting essentially of natural compound luteolin to provide prevention of the development of asthmatic features comprising Early Airway Response and Late Airway Response; and, it is therefore considered to anticipate the claimed method.

In the alternative, even if the claimed method is not identical to the referenced extract with regard to some unidentified characteristics, the differences between that which is disclosed and that which is claimed are considered to be so slight that the referenced method is likely to inherently possess the same characteristics of the claimed method particularly in view of the similar characteristics which they have been

shown to share. Thus, the claimed method would have been obvious to those of ordinary skill in the art within the meaning of USC 103. For instance, even if the claimed method of preventing and/or treating asthma in animals is not identical to the method taught by Aoyama with regard to preventing asthmatic features, *i.e.,* EAR and LAR; or modifying the levels of cellular constituents, *i.e.,* IFN-gamma, IL-5 and IL-4, or inhibiting airway constriction or airway hyperactivity; or the duration for the administration of luteolin; or the amount of the luteolin contained therein the referenced composition consisting essentially of luteolin is not in the same amount as instantly claimed by Applicant, it would have been obvious to one of ordinary skill in the art to modify the method of preventing and/or treating asthma in animals taught by Aoyama by modifying the amounts of the reference composition to be administered and the duration of the amounts of the reference composition to be administered to an animal in need thereof to provide the instantly claimed method of prophylaxis or treatment of asthma because at the time the invention was made it was known in the art that the administration of a composition consisting essentially of luteolin to animals had the claimed beneficial of altering the levels of IFN-gamma, IL-5, IL-4 and IgE provide an anti-asthmatic effect when administered to animals in need thereof, as evidenced by the teachings of Nagai and Kimata. Firstly, Nagai investigated the effects of an oriental-medical preparation comprising luteolin, *i.e.,* Sho-seiryu-to, and luteolin on bi-phase allergic reactions mediated by IgE. Nagai teaches administering Sho-seiryu-to once only or daily for a week significantly inhibited both immediate (Early Airway Response, EAR) and late phase reactions (Late Airway Response, LAR) in mice sensitized with

anti-DNP monoclonal IgE antibodies and DNP antigen. For example, Nagai teaches, "In immediate-phase instances, Sho-seiryu-to is thought to have effected inhibition by antagonistic operations against mediators, such as histamines released from mast cells. In late-phase cases, it is thought to have inhibited by suppressing the production and operation of cytokines [such] as TNF-alpha." Similarly, Nagai taught that administration of small quantities of luteolin demonstrated significant inhibitory effects on both immediate- and late-phase reaction, as well as, the release of histamine. Secondly, Kimata taught treating human cultured mast cells sensitized with IgE with luteolin before challenge with antihuman IgE inhibited the release of histamine, leukotrienes, prostaglandin D2, and granulocyte macrophage-colony stimulating factor in a concentration-dependent manner, which indicates that the administration of therapeutically effective amounts of a composition consisting essentially of luteolin to a subject in need of such treatment is effective in the treatment of asthma, as well documented and demonstrated by Nagai. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to modify the method of prophylaxis and/or treatment taught by Aoyama by adjusting the therapeutic amounts of the reference composition consisting essentially of a therapeutically effective dose of luteolin to be administered and the duration of the amounts of the reference composition to be administered to an animal in need thereof to provide the instantly claimed method of prophylaxis or treatment of asthma because at the time the invention was made it was known in the art that the administration of luteolin to animals including humans had the

claimed beneficial functional effect of altering the levels of the claim-designated components which are well-known mediators in the development of asthma (as readily admitted by Applicant on page 1, lines 23-28 of the present application) to provide the claimed method of prophylaxis and/or treatment asthma in animals because Aoyama teaches a method of treating asthma comprising administering therapeutic effective amounts of luteolin obtained from natural plant sources; and, Nagai and Kimata taught that therapeutic effective amounts of luteolin have the beneficial effect of mediating the levels of cellular components known to effect the development of asthmatic features.

Thus, it would have been a matter of judicious selection to one of ordinary skill in the art to modify the amounts and the duration of the amounts of luteolin administered to a patient in need thereof to provide a therapeutically effective dose of a composition consisting essentially of a therapeutically effective dose of luteolin to provide an immunomodulatory result effect variable since at the time the invention was made it was known in the art of medicine that the claim-designated limitations were known biochemical and biological mechanisms affecting the development or reduction of asthmatic symptoms and since luteolin was known to exhibit therapeutic activity in the treatment thereof. The claimed invention is no more than the routine optimization of a result effect variable. Thus, the claimed methods would have been obvious to those of ordinary skill in the art within the meaning of USC 103.

The United States Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether on not Applicants' method differs and, if so, to what extent, from that discussed in the references. Therefore, with the showing

of the references, the burden of establishing non-obviousness by objective evidence is shifted to Applicants.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Accordingly, the claimed invention as a whole was at least *prima facie* obvious, if not anticipated by the reference, especially in the absence of sufficient, clear, and convincing evidence to the contrary.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is 571-272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michele Flood
Primary Examiner
Art Unit 1655

MCF
October 14, 2005

Michele C. Flood
MICHELE FLOOD
PRIMARY EXAMINER